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Original Article

Bloodstream infections in hospitalized adults with dengue fever: Clinical characteristics and recommended empirical therapy

Ling-Shan Syue [a,b], Hung-Jen Tang [c,d], Yuan-Pin Hung [e], Po-Lin Chen [a,b], Chia-Wen Li [a,b], Ming-Chi Li [a,b], Pei-Fang Tsai [f], Ching-Chuan Liu [b,g,h], Nan-Yao Lee [a,b,h,**], Wen-Chien Ko [a,b,h,*]

[a] Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan
[b] Centre for Infection Control, National Cheng Kung University Hospital, Tainan, Taiwan
[c] Department of Medicine, Chi Mei Medical Center, Tainan, Taiwan
[d] Department of Health and Nutrition, Chia Nan University of Pharmacy & Science, Tainan, Taiwan
[e] Department of Internal Medicine, Tainan Hospital, Ministry of Health and Welfare, Tainan, Taiwan
[f] Departments of Pathology, National Cheng Kung University Hospital, Tainan, Taiwan
[g] Departments of Pediatrics, National Cheng Kung University Hospital, Tainan, Taiwan
[h] Department of Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan

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Empirical therapy;
Concurrent infection;
Fatality

Abstract *Background:* Dengue is an important mosquito-borne tropical viral disease and dual infection, though rare, has been regarded as a risk factor for severe disease and mortality. However, few studies focused on bloodstream infections (BSIs) and empirical antibiotic therapy rarely addressed.
Methods: Dengue patients with concurrent or subsequent BSIs between July 1 and December 31, 2015 were included. Clinical information, laboratory data, and drug susceptibility data were collected.
Results: Totally 80 patients, with an in-hospital mortality rate of 32.5%, were included and categorized into three groups. 32 patients in Group I (BSI onset within 48 h after admission), 32 in Group II (between 48 h and one week), and 16 in Group III (more than one week). Patients in Group I were older (mean age: 75.6 *vs.* 72.6 or 69.6 years; $P = 0.01$) and had a higher Charlson comorbidity index (3.1 *vs.* 1.8 or 1.9; $P = 0.02$) than those in Group II or III. *Streptococcus* species (28.9%, 11/38) and *Escherichia coli* (23.7%, 9/38) were major pathogens in Group I. *Enterobacteriaceae* (38.2%, 13/34) isolates predominated in Group II. Fatal patients more

* Corresponding author. Division of Infectious Diseases, Department of Internal Medicine, National Cheng Kung University Hospital, No. 138, Sheng Li Road, Tainan, 70403, Taiwan. Fax: +886 6 2752038.
** Corresponding author. Division of Infectious Diseases, Department of Internal Medicine, National Cheng Kung University Hospital, No. 138, Sheng Li Road, Tainan, 70403, Taiwan. Fax: +886 6 2752038.
E-mail addresses: nanyao@mail.ncku.edu.tw (N.-Y. Lee), winston3415@gmail.com (W.-C. Ko).

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often received inappropriate empirical antibiotic than the survivors (61.5% *vs.* 35.2%; $P = 0.03$). According to susceptibility data, pathogens in Group I and II shared similar susceptibility profiles, and levofloxacin, cefepime, or piperacillin/tazobactam, can be empirically prescribed for those hospitalized within one week.
Conclusions: BSI pathogens vary among dengue patients. For adults with dengue and suspected BSI hospitalized within one week, empirical antimicrobial agents are recommended.

Introduction

Dengue is a well-known mosquito-borne viral infection and endemic in tropical and sub-tropical areas. It causes more than 50 million infections annually worldwide and results in many hospitalization and deaths among children and adults among some countries.[1] Dengue is also endemic in Taiwan, and its incidence increased dramatically in recent years.[2,3] Clinical manifestations of dengue range from asymptomatic, self-limiting infection to severe, profound hemorrhagic shock and life-threatening condition. In 2015, a dengue outbreak occurred in Tainan, a modern metropolis of 1.88 million citizens at southern Taiwan, and a total of 22,777 indigenous cases were identified according to Taiwan's Centers for Disease Control (Taiwan CDC) report.[4] The outbreak in Tainan resulted in more than thousands of hospitalizations and caused tremendous healthcare burden. Management for dengue includes adequate fluid supply, best supportive care, and blood component transfusion, if necessary. However, some patients may progress to severe dengue or presented with other complications, including intractable internal bleeding, concurrent bacterial infection, multiorgan failure, which need aggressive therapy. Antimicrobial agent is not recommended as routine treatment for the cases of dengue virus infection. However, if BSIs developed in patients with dengue, timely antimicrobial agent use is important for better outcome. Possible risk factors or associated laboratory findings for identification of concurrent bacterial infection have been developed in previous studies, but appropriate empirical antibiotic regimen was not mentioned previously.[5–7] Besides, data about subsequent bacterial infection is sparse and seldom emphasize before. To answer this question, we conducted a retrospective study to survey common pathogens and drug susceptibility report in patients with dengue and concurrent or subsequent BSIs.

Methods

Study design and data collection

A retrospective study was conducted at three dengue referral hospitals, including two medical centers and one regional hospital, where nearly 60% of dengue patients during the outbreak in Tainan between August 1 and December 31, 2015, were cared. Adults (aged $\geq$ 18 years) with laboratory-confirmed dengue and BSI during the same hospitalization were included. Confirmatory tools for dengue included in serum the detection of dengue nonstructural protein 1 (NS1) antigen (SD 26 Dengue NS1+Ab Combo™, Standards Diagnostics, Korea), RNA of dengue virus by polymerase chain reaction (PCR), or anti-dengue immunoglobulin M by enzyme-linked immunosorbent assay (ELISA).[8] The blood culture system used was BACTEC 9240 (Beckon Dickinson, Sparks, MD, USA), and bacterial identification and drug susceptibility were performed by the Vitek2 system (bioMérieux, Lyon, France). Interpretation of antimicrobial susceptibility reports was based on the standards of the Clinical and Laboratory Standards Institute in 2014.[9] Ampicillin-sulbactam, piperacillin-tazobactam, cefotaxime, cefepime, and levofloxacin were tested for available isolates. In addition, cefazolin, ceftazidime, ciprofloxacin, imipenem, meropenem, amikacin, gentamicin, and trimethoprim/sulfamethoxazole were tested for Gram-negative pathogens. The growth of coagulase-negative staphylococci (CoNS), *Propionibacterium* or *Micrococcus* species in one of at least two sets of blood cultures was regarded as blood culture contamination.[10] Clinical data were collected by chart review and analyzed anonymously.

Definitions

The included patients were categorized as three groups, according to the time between admission and BSI onset. Group I was defined as the BSI episodes detected within 48 h of admission, Group II between 48 h and seven days, and Group III eight or more days after admission. Group I was regarded as community-onset bacteremia, indicative of the acquisition of the pathogens within 48 h of admission,[11] and the others as hospital-onset bacteremia. If the onset date of fever was clearly indicated in medical records, it was referred as the date of dengue onset. If patients were transferred between study hospitals, the hospital course in these hospitals was regarded as the same hospitalization. The definitions of comorbidities were mentioned previously and the severity of the bloodstream infection was assessed by the Pittsburgh bacteremia score.[12,13] Patients suffering from gastrointestinal bleeding at the timing of BSI episode detection were defined as concurrent gastrointestinal bleeding.

Multidrug-resistant pathogens are defined as penicillin-resistant streptococci, ampicillin-resistant enterococci, methicillin-resistant staphylococci, third generation cephalosporin-resistant Gram-negative pathogens, and fungus. Empirical antimicrobial therapy was referred to the

drugs prescribed continuously for at least 48 h after the BSI onset. If they were *in vitro* active against the causative pathogen, they were defined as being appropriate. In contrast, empirical therapy was regarded as being inappropriate, if the causative pathogen was *in vitro* resistant to the prescribed drugs, or no antimicrobial agent was prescribed with 24 h after blood cultures were sampled.

Dengue severity was defined according to the 2009 WHO guideline, which classified symptomatic dengue virus infection as dengue with and without warning signs and severe dengue.[14] Warning signs includes abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy, restlessness, hepatomegaly (liver enlargement >2 cm) and an increase in the hematocrit, concurrent with a rapid decrease in the platelet count. Severe dengue was diagnosed in those patient with severe plasma leakage (shock or fluid accumulation leading to respiratory distress), severe hemorrhage, or severe organ impairment (acute hepatitis with alanine and/or aspartate aminotransferease >1000 U/L, impaired consciousness, acute kidney injury with rapid increase in serum creatinine level > 0.5 mg/dL, or heart damage).

Statistical analysis

Statistical analyses were performed by the SPSS, version 20.0 (SPSS, Chicago, IL, USA). Pearson's Chi-square test or two-tailed Fisher's exact test was used to examine nominal data and unpaired Student's *t* test for continuous data. Risk factors for mortality were examined by the univariate analysis and adjusted by means of the multivariate logistic regression analysis. A *P* value of less than or equal to 0.05 was regarded as statistically significant.

Results

Between July 1, 2015 and December 31, 2015, total 80 patients with dengue and BSI were included. Sixty-three patients were treated in two medical centers, including 22 patients in a published study,[15] and 17 in a regional hospital in Tainan. Nearly a half (41, 51.3%) patients were males. Most (86%) patients were the elderly aged at least 65 years, and their mean age was 73.2 years old. With regard to the time between the initial onset of dengue to BSI onset, excluding two patients without definitive timing of dengue onset, 17 (21.8%) of 78 patients developed BSI within 48 h of dengue onset, and 51 (65.4%) within one week. In average, BSI was noted in 7.8 days after dengue onset.

There were 32 (40%), 32 (40%), and 16 (20%) patients in Group I, II, and III, respectively. Baseline characteristics, laboratory data, and clinical outcomes of these patients were listed in Table 1. Group I tended to be older than Group II or III (75.6 ± 7.4 *vs.* 72.6 ± 9.4 *vs.* 69.6 ± 11.7 years; $P = 0.10$) and had a higher Charlson comorbidity index (3.1 ± 2.3 *vs.* 1.8 ± 1.7 *vs.* 1.9 ± 1.5; $P = 0.02$). Group I and II tended to less often suffer from leukocytosis at BSI onset (11/32, 34.4% *vs.*12/32, 37.5% *vs.* 9/16, 56.3%; $P = 0.32$), but more often thrombocytopenia (25/32, 78.1% *vs.* 28/32, 87.5% *vs.* 9/16, 56.3%; $P = 0.05$) and concurrent gastrointestinal bleeding (15/32, 46.9% *vs.* 14/32, 43.8% *vs.* 3/16, 18.8%; $P = 0.15$) than Group III. Additionally, the receipt of antimicrobial therapy before BSI onset outnumbered in Group III (12/16, 75% *vs.* Group I: 1/32, 3.1% *vs.* Group II: 10/32, 31.3%; $P < 0.001$). All but one discharged against medical advice in Group III had longer hospitalization than Group I or II (in average 44 days) due to complications after dengue onset, such as prolonged gastrointestinal bleeding for more than one week (7 patients), prolonged ventilator support (4), renal failure requiring renal replacement therapy (2), perforated peptic ulcer (1), and ischemic bowel (1).

All patients had blood cultures performed at the emergence department and initial blood cultures were sterile in Group II and III. Blood cultures were sampled in Group II due to recurrent fever (12, 37.5%), prolonged fever (10, 31.3%), or unstable hemodynamic condition (10, 31.3%). In Group II, 27 (84.3%) patients developed BSI after the nadir of leukocyte count (mean 2900 cells/mm^3, 800–6600 cells/mm^3) and the average duration between the leukocyte nadir and BSI onset was 1.9 days. All blood cultures collected in Group III were due to febrile events.

A total of 86 bacterial isolates (29 Gram-positive isolates and 57 Gram-negative isolates) and four *Candida* isolates were obtained from eighty patients. Sixty-seven (83.7%) patients had monomicrobial bacteremia, nine (11.3%) polymicrobial bacteremia, and four (5%) candidemia. Of those with polymicrobial bacteremia, five had Gram-positive and Gram-negative co-infection, and four polymicrobial Gram-negative BSIs.

All isolated organisms were categorized into three groups as previous definition in Table 2. Of 38 bacteremic isolates in Group I, *Streptococcus* species (11, 28.9%) were most common and only one isolate of *Streptococcus salivarius* was resistant to penicillin. Nearly a half (55.3%) of the pathogens in Group I were Gram-negative bacilli, including ten *Enterobacteriaceae* isolates, nine glucose-non-fermenting Gram-negative bacilli, including *Pseudomonas aeruginosa* and *Acinetobacter* species, and two *Moraxella* isolates. Among 19 Gram-negative pathogens with CLSI susceptibility interpretation criteria, five (26.3%) isolates were resistant to third generation cephalosporins.

Of 34 bacteremic isolates from 32 patients in Group II, *Enterobacteriaceae* isolates (13 isolates, 38.2%) were dominant, followed by *Streptococcus* species (4 isolates), Methicillin-susceptible *Staphylococcus aureus* (3), *P. aeruginosa* (3), and *Acinetobacter* species (3). More than one-fifth (22.8%) of GNB isolates were resistant to third generation cephalosporins. All four *Streptococcus* isolates were susceptible to penicillin and only one coagulase-negative staphylococcal isolate was methicillin-resistant. Two *Candida* isolates resistant to any antibacterial agents were identified.

Of 18 BSI pathogens in Group III, Gram-negative isolates (13, 72.2%) outnumbered Gram-positive isolates (3, 16.7%). There were three carbapenem-resistant *Elizabethkingia meningoseptica*, two vancomycin-resistant *Enterococcus faecium*, and two *Candida* isolates. Moreover, seven (53.8%) of thirteen Gram-negative isolates were resistant to 3rd generation cephalosporins and overall MDR pathogens accounted 67% (12/18) in Group III.

Of all bacteremic pathogens, excluding three *Moraxella* isolates and four *Candida* isolates, antimicrobial susceptibility data for 83 isolates were shown in Fig. 1. Of

Table 1 Clinical characteristics and outcomes of 80 hospitalized adults with dengue fever and bloodstream infection (BSI) categorized by the time between admission and BSI onset.

Characteristics	All cases n = 80	Group I n = 32	Group II n = 32	Group II n = 16	*P* value
Age, years	73.2 ± 9.4	75.6 ± 7.4	72.6 ± 9.4	69.6 ± 11.7	0.10
Male	41 (51.3)	15 (46.9)	19 (59.4)	7 (43.8)	0.48
Comorbidities					
Charlson comorbidity index	2.4 ± 2.0	3.1 ± 2.3	1.8 ± 1.7	1.9 ± 1.5	0.02
Hypertension	59 (73.8)	28 (87.5)	20 (62.5)	11 (68.8)	0.07
Diabetes mellitus	41 (51.3)	18 (56.3)	13 (40.6)	10 (62.5)	0.28
Chronic kidney disease	21 (26.3)	9 (28.1)	9 (28.1)	3 (18.8)	0.75
Coronary artery disease	16 (20)	6 (18.8)	7 (21.9)	3 (18.8)	0.94
Cerebrovascular disease	10 (12.5)	6 (18.8)	3 (9.4)	1 (6.3)	0.37
Malignancy	16 (20)	10 (31.3)	4 (12.5)	2 (12.5)	0.12
Clinical condition & disease severity					
Admission to BSI, days	5.8 ± 8.5	0.4 ± 0.8	4.8 ± 1.2	18.4 ± 11.9	<0.0001
DF onset to BSI[a], days	7.8 ± 8.7	2.3 ± 1.9	6.9 ± 2.0	20.6 ± 11.7	<0.0001
Concurrent gastrointestinal bleeding	32 (40.0)	15 (46.9)	14 (43.8)	3 (18.8)	0.15
Leukocytosis (≥9000/mm^3) at BSI onset	32 (40.0)	11 (34.4)	12 (37.5)	9 (56.3)	0.32
Thrombocytopenia (≤100,000/mm^3) at BSI onset	62 (77.5)	25 (78.1)	28 (87.5)	9 (56.3)	0.05
Antibiotic usage before BSI	23 (28.8)	1 (3.1)	10 (31.3)	12 (75.0)	<0.0001
Multiple drug resistant pathogens	28 (35.0)	8 (25.0)	8 (25.0)	12 (75.0)	0.001
Inappropriate empirical antibiotic	35 (43.8)	14 (43.8)	10 (31.3)	11 (68.8)	0.05
Pitt bacteremia score ≥4 at BSI onset	30 (37.5)	13 (40.6)	12 (37.5)	5 (31.3)	0.82
APACH II score while BSI event	19.6 ± 11.8	22.0 ± 12.6	19.6 ± 12.3	14.8 ± 7.1	0.13
Clinical outcomes					
Total length of hospitalization	17.4 ± 20.6	9.1 ± 8.2	12.1 ± 8.2	44.4 ± 31.3	<0.0001
Severe dengue	48 (60.0)	19 (59.4)	18 (56.3)	11 (68.8)	0.70
Intensive care unit admission	41 (51.2)	16 (50.0)	15 (46.9)	10 (62.5)	0.58
Ventilation failure	27 (33.8)	10 (31.3)	10 (31.3)	7 (43.8)	0.64
In-hospital mortality	26 (32.5)	12 (37.5)	10 (31.3)	4 (25.0)	0.67

[a] Definitive timing of dengue onset could not be identified in two patients.
Data are shown as case number (%), mean ± standard deviation.

five antibiotics, only levofloxacin was active against more than 80% of all bacterial pathogens tested (susceptible rate in Group I, II, and III: 81.8%, 86.2%, and 81.3%). Cefepime and piperacillin/tazobactam had better antibacterial activity against pathogens in Group I and II than those in Group III (cefepime: 86.1% and 87.1% *vs*.50.0%; piperacillin/tazobactam: 83.3% and 77.4% *vs*.50.0%), while cefotaxime without coverage of *P. aeruginosa* and *Acinetobacter* species showed poor activity (susceptible rate: 72.2% and 67.7% *vs*. 31.3%). In summary, levofloxacin, piperacillin/tazobactam, and cefepime present a better coverage of bacterial pathogens identified within one week (susceptibility rate in Group I and II *vs*. Group III: levofloxacin 83.9% *vs*.81.3%, piperacillin/tazobactam 80.6% *vs*.50.0%, and cefepime 86.4% *vs*. 50.0%). When focusing on Gram-negative pathogens, drug susceptibility for these isolates varied greatly, but pathogens in Group I and II exhibited similar susceptibility profiles for most antibiotics tested (Fig. 2).

About one half (41, 51.2%) patients needed intensive care and 48 (60.0%) progressed to severe dengue. The overall case fatality rate was 32.5%, while patients in Group I tended to have a higher fatality rate than those in Group II and Group III (37.5% *vs*. 31.3% and 25.0%; $P = 0.67$) (Table 1). Fatal patients more often had critical illness with a high Pitt bacteremia score at BSI onset (≥4: 96.2% *vs*. 9.3%; $P < 0.001$), were infected by multidrug-resistant pathogens (50.0% *vs*. 27.8%; $P = 0.05$), and received inappropriate empirical antibiotic (61.5% *vs*. 35.2%; $P = 0.03$) than surviving patients. This trend was similar in those in Group I and II, who developed BSI within one week after admission, as shown in Table 3.

Discussion

To the best of our knowledge, our study included a larger case number (32 cases) of dengue and concurrent BSIs, as compared with two previous studies.[6,7] Besides we included subsequent BSIs and analyzed BSI pathogens to formulate optimal empirical therapy. As for the causative species of BSIs, *S. aureus*, *Salmonella typhi*, and *Escherichia coli* had been reported to be major pathogens among 29 Singapore patients with BSIs detected within 72 h of admission.[7] See et al. recognized 110 episodes of bacterial coinfection developing within 48 h after hospital arrival from 83 patients, including 25 episodes of bacteremia. Major bacteremic pathogens were *S. aureus* (five methicillin-susceptible and three methicillin-resistant *S. aureus* isolates), *E. coli* (n = 6) and *Klebsiella pneumoniae* (n = 3), but

Table 2 A total of 90 bloodstream isolates from 80 hospitalized adults with dengue fever categorized by the time between admission and bloodstream infection (BSI) onset.

Pathogens	Isolate number (%)			
	All isolates n = 90	Group I n = 38	Group II n = 34	Group III n = 18
Gram-positive pathogens	29 (32.0)	17 (44.7)	9 (13.2)	3 (16.7)
Streptococcus species	15 (16.7)[a]	11 (28.9)	4 (11.8)	0 (0)
Enterococcus species	6 (6.7)	2 (5.3)[b]	1 (2.9)[b]	3 (16.7)[c]
Methicillin-susceptible *Staphylococcus aureus*	4 (4.4)	1 (2.6)	3 (8.8)	0 (0)
Methicillin-susceptible *Staphylococcus epidermidis*	2 (2.2)	2 (5.3)	0 (0)	0 (0)
Methicillin-resistant *Staphylococcus aureus*	1 (1.1)	1 (2.6)	0 (0)	0 (0)
Methicillin-resistant coagulase-negative staphylococci	1 (1.1)	0 (0)	1 (2.9)	0 (0)
Gram-negative pathogens	57 (63.3)	21 (55.3)	23 (67.6)	13 (72.2)
Escherichia coli	14 (15.6)	9 (23.7)	4 (11.8)	1 (5.6)
Pseudomonas aeruginosa	8 (8.9)	3 (7.8)	3 (8.8)	2 (11.1)
Acinetobacter species	8 (8.9)[d]	3 (7.8)	3 (8.8)	2 (11.1)
Klebsiella pneumoniae	7 (7.8)	1 (2.6)	5 (14.7)	1 (5.6)
Elizabethkingia meningoseptica	3 (3.3)	0 (0)	0 (0)	3 (16.7)
Aeromonas species	3 (3.3)[e]	0 (0)	3 (8.8)	0 (0)
Salmonella species	2 (2.2)	0 (0)	1 (2.9)	1 (5.6)
Enterobacter cloacae	2 (2.2)	0 (0)	1 (2.9)	1 (5.6)
Others	10 (11.1)	5 (13.2)[f]	3 (8.8)[g]	2 (11.1)[h]
Candida species	4 (4.4)	0 (0)	2 (5.9)	2 (11.1)

[a] Viridans streptococci (13 isolates), *S. agalactiae* (1), and *S. dysgalactiae* (1).
[b] Ampicillin-susceptible *E. faecalis* (3).
[c] Vancomycin-resistant *E. faecium* (2) and ampicillin-resistant *E. faecium* (1).
[d] *A. baumannii* (7) and *A. junii* (1).
[e] *A. caviae* (2) and *A. dhakensis* (1).
[f] *Moraxella urethralis* (1), *Moraxella osloensis* (1), *Ralstonia pickettii* (1), *Shewanella putrefaciens* (1), and *Myroides* species (1).
[g] *Moraxella* species (1), *Proteus mirabilis* (1), and *Serratia marcescens* (1).
[h] *Morganella morganii* (1) and *Chryseobacterium indologenes* (1).

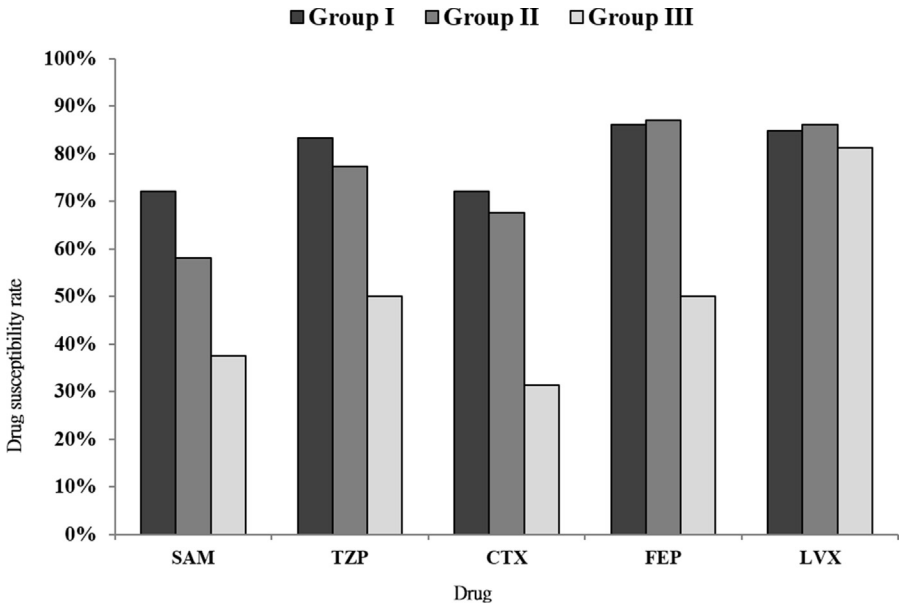

Figure 1. Susceptibility data of five antimicrobial agents for 83 bacteremic isolates from the hospitalized adults with dengue fever, except levofloxacin for 78 isolates (excluding 3 *Staphylococcus* and 2 *Streptococcus* isolates)*. *Three *Moraxella* isolates were excluded for susceptibility tests due to no interpretation criteria and five gram-positive isolates were not available for susceptibility tests. CTX = cefotaxime; FEP = cefepime; LVX = levofloxacin; SAM = ampicillin-sulbactam; TZP = piperacillin-tazobactam.

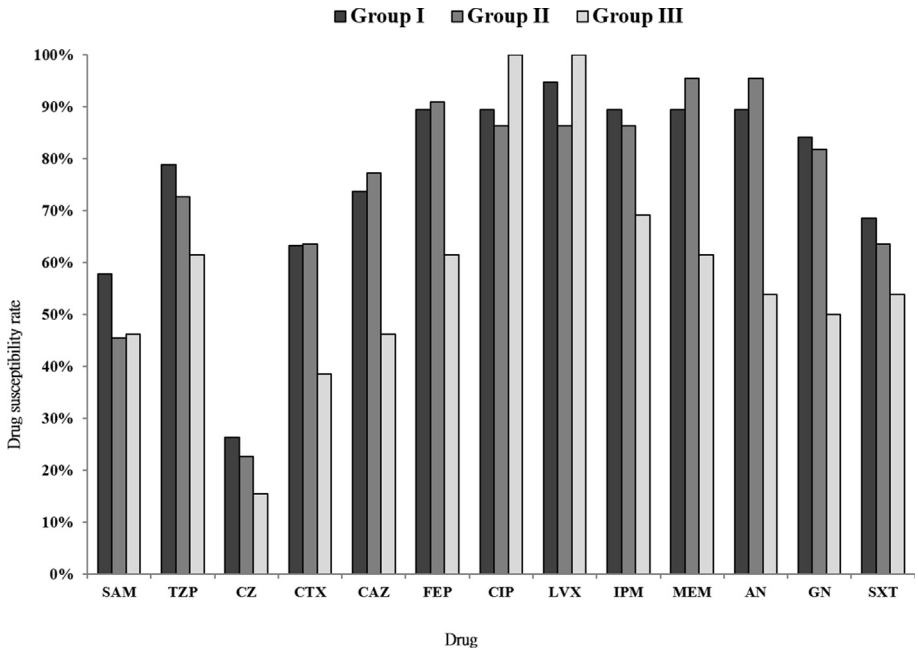

Figure 2. Susceptibility data of 13 antimicrobial agents for 54 g-negative bacteremic isolates from the hospitalized adults with dengue fever*. *Three *Moraxella* isolates were excluded for susceptibility tests due to no interpretation criteria. AN = amikacin; CAZ = ceftazidime; CIP = ciprofloxacin; CTX = cefotaxime; CZ = cefazolin; FEP = cefepime; LVX = levofloxacin; IPM = imipenem; MEM = meropenem; SAM = ampicillin-sulbactam; SXT = trimethoprim-sulfamethoxazole; TZP = piperacillin-tazobactam.

Table 3 Risk factors of in-hospital mortality among 80 hospitalized adults with dengue fever and bloodstream infection (BSI).

Characteristics	All patients, n = 80			Group I and II[a], n = 64		
	Surviving n = 54	Fatal n = 26	*P* value	Surviving n = 42	Fatal n = 22	*P* value
Age (mean ± SD), years	72.5 ± 9.4	74.7 ± 9.5	0.35	73.3 ± 8.7	75.8 ± 8.2	0.27
Charlson comorbidity index (mean ± SD)	2.1 ± 2.0	3.0 ± 1.8	0.07	2.2 ± 2.2	3.1 ± 1.8	0.12
Multidrug-resistant pathogens	15 (27.8)	13 (50.0)	0.05	7 (16.7)	9 (40.9)	0.03
Inappropriate empirical antibiotic therapy	19 (35.2)	16 (61.5)	0.03	12 (28.6)	12 (54.5)	0.04
Pitt bacteremia score ≥ 4 at BSI onset	5 (9.3)	25 (96.2)	0.00	3 (7.1)	22 (100)	0.00

[a] Defined as patients developed BSI within one week after hospital arrival.
SD = standard deviation.

P. aeruginosa or *Acinetobacter* species also were noted.[6] In contrast, our study noted *Streptococcus* species (n = 11) were major pathogens in patients with dengue and BSI within 48 h. As described previously, *P. aeruginosa* (n = 3) and *Acinetobacter* species (n = 3) were identified in such a clinical setting, and two patients with *P. aeruginosa* BSI and one with *Acinetobacter* BSI had no recent hospitalization, nursing home residence, antibiotic exposure, or invasive procedure history. Although among our study and two studies in Singapore including BSI events within 48 h, dominant pathogens varied, it is worthy to highlight the finding that glucose non-fermenting gram-negative bacilli, such as *P. aeruginosa* or *Acinetobacter* species, should be put into the list of causative pathogens of BSIs, even though these patients have no traditional risk factors of healthcare-associated infections.

While the pathogenesis of dengue virus infection had been investigated thoroughly, little is known about the host factors related to concurrent bacterial infections in the individuals with dengue virus infection.[16–18] Proposed hypotheses include induced weakened immunity, endothelial cell dysfunction and apoptosis, vascular permeability increase, or mucocutaneous or intestinal mucosal injury facilitating microbial translocation.[19,20] Nearly a half (15, 47%) of 32 patients in Group I experienced concurrent severe gastrointestinal bleeding, which was, at least partially, consistent with the above hypothesis. The hypothesis of mucocutaneous or intestinal mucosal injury associated with bacterial translocation is related to the fact that many bacterial pathogens, such as staphylococci, streptococci, or *Enterobacteriaceae*, are the commensals in skin or oral mucosa or intestine,[5–7] and also dominant pathogens in our patients with dengue and concurrent BSIs. Moreover, we reported two cases of BSIs due to *Moraxella* species, normal commensals of human upper respiratory tract, which was regarded as the bacteremic pathogen in

two case reports[21,22] and a case series.[5] The above clinical data and our study finding support its etiological role of invasive infection.

However, microbial translocation alone could not well explain all events of concurrent BSIs in dengue patients, since rare pathogens, such as *Leptospira*, *Stenotrophomonas maltophilia*, *Kluyvera cryocrescens*, or *Rosemonas* species, have been reported.[5,6,23,24] Dengue virus has been recognized to increase the susceptibility of *S. aureus* or *P. aeruginosa* infection in the *Drosophila* model.[25] Besides, dengue virus may cause transient suppression of host innate immune system.[26] Weakened host immunity and progressive leukopenia during dengue virus infection might explain, at least partially, the occurrence of BSIs due to bacterial pathogens.

Prior studies often focused on concurrent bacterial infection, but rarely addressed subsequent BSI events in dengue. Patients with subsequent BSIs contributed considerable fatality, since 84% of the patients in Group II developed BSIs following the nadir status of leukopenia. Prolonged or recurrent fever and hypotension/shock might be the hints of BSIs in Group II and blood cultures should be obtained. Furthermore, 44% of the patients in Group II experienced concurrent gastrointestinal bleeding, suggestive of microbial translocation as the potential pathogenesis of concurrent bacterial infection in dengue. Comparing with Group I, Group II patients had longer hospital stay before BSI onset, more antibiotic exposure, and more Gram-negative pathogens. Because of the resemblance of antimicrobial susceptibility profiles of bacteremic pathogens in both groups, we recommend similar empirical antibiotic regimens.

Of note, two cases of *C. tropicalis* BSI were noted on day 5 and day 7 after admission. One patient had underlying disease of hepatitis B virus-related cirrhosis and hepatocellular carcinoma, and the other had been in end stage of renal disease receiving regular hemodialysis for more than five years. Both had no recent hospitalization and had initial sterile blood cultures sampled at ER, but later suffered from severe gastrointestinal bleeding and hemorrhagic shock and received broad-spectrum antibiotics for at least three days before the event of BSIs. Candidemia, rarely reported in the literature,[27] should be considered in the elderly with dengue and exposure to broad-spectrum antibiotics, even within the first week of hospitalization.

No relevant data discussing empirical antimicrobial therapy for suspected BSIs in the individuals with severe dengue were reported before. As well known in sepsis control guideline, adequate antimicrobial treatment is associated with better outcome.[28,29] In accordance to the literature, our patients with severe dengue with concurrent or subsequent BSIs would have a poor prognosis, if not empirically treated by appropriate antibiotics. To cover at least 80% of both Gram-positive and Gram-negative pathogens in BSIs occurring within one week of hospitalization, levofloxacin, cefepime, or piperacillin/tazobactam can be suggested as the empirical antibiotic option. Due to varied resistance profiles of Gram-negative isolates and patient characteristics, empirical therapy for the patients in Group III should be based on recent antibiotic exposure and local susceptibility data, and be adjusted when susceptibility reports are available.

With the nature of a retrospective clinical study, some limitations were present in our study. First, though BSI episodes in Group I were reasonably regarded as community-onset infections, one fourth of 32 patients were infected by multidrug-resistant pathogens. However, prior antibiotic exposure could be traced in only one patient (Table 1). With old age (mean age of 76 years) and a high Charlson comorbidity index in the patients of Group I, more exposure to the healthcare system and antibiotics were likely to be related to the occurrence of BSIs due to glucose non-fermenting Gram-negative bacilli or multidrug-resistant pathogens. Second, suboptimal glycemic control in diabetic cases has been demonstrated to be linked to non-shock dengue hemorrhagic fever, dengue shock syndrome, severe dengue,[30] and community-onset BSIs.[31] However, because of the retrospective nature in our study, the degree of glycemic control in adults with diabetic mellitus, accounting for nearly a half of the study cohort, were not completely assessed. The interaction of BSIs, diabetes mellitus, and dengue fever warrants further investigations. Third, the distribution of BSI pathogens and their antimicrobial susceptibility data in non-dengue patients during the same period were not accessed. It is not clear that BSI pathogen distribution in three groups were unique or similar to that of other patients in the study hospitals. However, such microbiological and clinical information will be useful for primary care of hospitalized adults with dengue fever. Finally, the need of blood cultures was at the discretion of attending physicians, and such a clinical practice may underestimate the incidence of BSIs. However, at least in the cases of severe dengue admitted to ICUs, BSIs were noted in a similar percentage in two medical centers, 24.0% (18 of 75 patients)[32] and 23.1% (33 of 143 patients),[33] highlighting a significant risk of BSIs among critical adults with dengue fever.

Unlike the predominance of pediatric patients in southeast Asia, dengue in Taiwan mainly affects adults, esp. the elderly who suffer from more complications and be at a high risk of bacterial co-infections.[34,35] Thus in the dengue outbreak in Tainan, BSIs in the elderly contribute substantial fatality. In conclusion, not only Gram-positive and Gram-negative bacteria, including non-*Enterobacteriaceae* pathogens, but also *Candida* species, though rarely, should be put into the list of potential pathogens during hospitalization. Empirical antibiotic regimen, such as levofloxacin, cefepime, or piperacillin/tazobactam, is recommended for the BSI events within one week's hospitalization.

Competing interests

All authors declare no conflicts of interest.

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